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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WILLIAM H. BOSCH, MATTHEW R. HILBORN, DOUGLAS C. HOVEY, LAURA J. KLINE, ROBERT W. LEE, JOHN D. PRUITT, NIELS P. RYDE, TUULA A. RYDE, and SHUQIAN XU

Appeal 2010-011060
Application 10/619,539
Technology Center 1600

Before RICHARD TORCZON, ROMULO H. DELMENDO, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52 begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

This is a decision on the appeal under 35 U.S.C. § 134 by the Patent Applicants from the Patent Examiner's rejections of claims 1-3, 5-35, 37, 39, 41, and 43-45. The Board's jurisdiction for this appeal is under 35 U.S.C. §§ 6(b). We affirm.

STATEMENT OF THE CASE

The claims are directed to stable nanoparticulate liquid dosage compositions. According to the Specification, nanoparticulate liquid dosage compositions can be prone to crystal growth (Spec. 4:29-30). The Specification states:

> the invention is directed to the surprising discovery that commonly used, non-toxic pharmaceutical ingredients which are osmotically active, such as glycerol, mannitol, and sodium chloride, can function as crystal growth inhibitors in liquid dosage compositions of nanoparticulate active agent.

(Spec. 8:5-9.)

The pending claims stand rejected by the Examiner as follows:

1. Claims 1-3, 5, 6, 8-19, 21-24, 27-29, 32-35, 37, 39, 41, and 43-45 under 35 U.S.C. § 102(b) as anticipated by Liversidge '401[2] (Answer 5);

2. Claims 1-3, 5-24, 26-31, 35, 37, 39, 41, and 43-45 under 35 U.S.C. § 102(e) as anticipated by Kipp '329[3] (*id.* at 7);

3. Claims 1-3, 5-24, 27-29, 32-35, 37, 39, 41, and 43-45 under 35 U.S.C. § 103 as obvious over Liversidge '041 in view of Brockbank[4] or Kipp '329 (*id.* at 8);

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[2] Method to Reduce Particle Size Growth During Lyophilization, U.S. Patent No. 5,302,401 (filed Dec. 9, 1992) (issued Apr. 12, 1994).
[3] Compositions of and Method for Preparing Stable Particles in a Frozen Aqueous Matrix, U.S. Patent Application No. 2003/0077329 (filed Oct. 11, 2002) (published Apr. 24, 2003).

4. Claims 25-35, 37, 39, 41, and 43-45 under 35 U.S.C. § 103 as obvious over Liversidge '041 and Liversidge '049[5] (*id.* at 9);

5. Claim 2 under 35 U.S.C. § 112, ¶ 1, as failing to comply with the enablement requirement (*id.* at 4); and

6. Claim 15 under 35 U.S.C. § 112, ¶ 2, as indefinite (*id.* at 4-5).

Claim 1 is representative and reads as follows:

> 1. A stable nanoparticulate liquid dosage composition comprising:
>
> (a) particles of at least one active agent having an effective average particle size of less than 2000 nm;
>
> (b) at least one surface stabilizer;
>
> (c) at least one osmotically active crystal growth inhibitor that is capable of preventing crystal growth of the active agent at ambient temperature, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharides [sic], a sugars [sic], a sugar alcohol, sodium chloride, potassium chloride, magnesium chloride, and an ionic salt; and
>
> (d) a liquid media [sic],
>
> wherein the liquid dosage composition does not incorporate a cloud point modifier.

FINDINGS OF FACT (FF)

Liversidge '401

1. Liversidge '401 describes a composition comprising:

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[4] Cyclohexanediol Cryoprotectant Compounds, International Publication No. WO 01/78505 (filed Apr. 17, 2001) (published Oct. 25, 2001).
[5] Novel Griseofulvin Compositions, U.S. Patent Application No. 2005/0004049 (filed Oct. 14, 2003) (published Jan.6, 2005).

2. nanoparticles containing a poorly soluble therapeutic or diagnostic agent (col. 1, ll. 53-54 & col. 2, ll. 1-5);

3. a surface modifier adsorbed on the surface the nanoparticles (col. 1, ll. 53-55);

4. a cryoprotectant (col. 1, ll. 55-56); and

5. a liquid medium (col. 5, ll. 43-44 & 52-53).

6. The average particles size is less than about 400 nm (col. 4, l. to col. 5, l. 14).

7. Liversidge '401 teaches that conventional lyophilization leads to agglomeration and growth in nanoparticle size, but the "invention describes the application of lyophilization to preparation of freeze-dried drug nanoparticles that retain their small particle size" and with "reduced or no particle size growth" (col. 1, ll. 19-30).

8. Liversidge '401 teaches:

> Cryoprotectants (cryoprotective agents or compounds) are agents that protect chemical compounds, cells, or tissues from the deleterious effects of freezing that may accompany lyophilization. In the case of nanoparticles, cryoprotectants protect from the agglomeration caused by the process of lyophilization, namely freeze-drying.

(Col. 5, ll. 20-26)

9. Liversidge '401 lists exemplary cryoprotectants, such as sucrose, mannitol, surface active agents such as the Tweens, and glycerol (col. 5, l. 27-33) and uses sucrose, mannitol, and Tween 80 in its examples (col. 6-col. 7).

10. In the examples, Liversidge '401 reported that Tween 80 or 2% mannitol in the original dispersion did not significantly decrease the large

particle size after reconstitution, but addition of 2% sucrose to the initial dispersion led reduced particle size during lyophilization.

Kipp '329

11. Kipp '329 describes a composition of a stable nanoparticle suspension of a poorly water soluble pharmaceutical agent suspended in a "frozen aqueous matrix" where the "freezing may circumvent" instability problems (Abstract; ¶¶ 39-40).

12. Kipp '329 describes methods of making nanoparticle suspensions in an aqueous matrix (¶ 46).

13. Kipp '329 teaches that its composition can comprise:

14. • surface modifiers (¶ 42);

15. • cryoprotectants (*id.*);

16. • osmotic agents (*id.*); and

17. • crystal growth modifiers (*id.*).

18. The nanoparticles are described as preferably less than about 2 µm, and even more preferably less 200 nm (¶ 78).

19. Cryoprotectants include sucrose, mannitol, glycerol, and Tweens (¶ 71).

20. Osmotic agents include mannitol, glycerol, and sodium chloride (¶ 73).

LEGAL PRINCIPLES

"To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

> In some cases, the inherent property corresponds to a claimed new benefit or characteristic of an invention otherwise in the prior art. In those cases, the new realization alone does not

> render the old invention patentable. *See Atlas Powder*, 190 F.3d at 1347 ("[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's function, does not render the old composition patentably new to the discoverer.").

Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1377 (Fed. Cir. 2005).

"[W]hen the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

ANTICIPATION BY LIVERSIDGE

Issue

The Examiner found that all four components a) through d) of claim 1 are described in Liversidge '401, anticipating the claimed composition (Answer 5-6; FF1-FF6). Appellants contend that the Examiner erred in finding that Liversidge '401 described the claimed subject matter.

Lyophilized composition

Appellants contend that Liversidge '401 describes a lyophilized composition, not a liquid composition as recited in claim 1 (App. Br. 9). Appellants contend that "the mixture of a suspension of drug nanoparticles and a solution of cryoprotectant is only an intermediate product rather than a final product" which is further processed by lyophilization (Reply Br. 8-9).

Liversidge '401 expressly described an aqueous composition (FF5). It is not removed from the prior art simply because it is an "intermediate" which is subsequently subjected to lyophilization. *In re Mullen*, 481 F.2d 1333, 1336 (CCPA 1973) ("the intermediate structure of Haigis was both

intended and appreciated. It matters not one whit that it was intended to be and appreciated as being an intermediate structure rather than an end use item.")

All elements not as arranged in the claim

Appellants contend "it is insufficient to support an anticipation rejection by merely pointing out certain claim elements in the cited reference. The Examiner is required to articulate how the elements are 'arranged as in the claim.'" (Reply Br. 9.)

Claim 1 is directed to composition comprising four components. The Examiner explained on pages 5-6 and 10 of the Answer how Liversidge '401 described all the components of claim 1 (FF1-FF6). Appellants did not identify an error in the Examiner's findings, and upon review, we find no defect in them.

Cryoprotectant of Liversidge '401 does not teach or suggest claimed crystal growth inhibitor

Appellants contend that Liversidge 401's description of a cryoprotectant does not teach or suggest the claimed crystal growth inhibitor. First, Appellants contend that cryoprotectants have a different function than crystal growth inhibitors (Reply Br. 10). Appellants state that crystal growth inhibitors prevent an increase in crystal size at ambient temperature, while cryoprotectants function during the freezing and lyophilization process (Reply Br. 10; FF7 & FF8). Consequently, they contend the ordinary skilled worker would not have been "led" by Liversidge '401 to pick a crystal growth inhibitor (Reply Br. 10). Second,

Appellants contend that Liversidge '401 lists mannitol and Tween as cryoprotectants, but Liversidge's shows that mannitol and Tween were not suitable in its working examples (*id.* at 11).

To be clear, the Examiner found that Liversidge '401's composition, prior to lyophilization, anticipated the claimed subject matter (Answer 5-6). This composition comprises cryoprotectants – including mannitol, a compound which is specifically claimed (claim 6) and used in certain examples described in Liversidge '401 (FF9 & FF10). While Liversidge '401 may not have appreciated that mannitol, or the other identified cryoprotectants, had additional properties in preventing crystal growth at ambient temperature, recognition of an inherent property is not a basis for patentability. *Perricone*, 432 F.3d at 1377.

Appellants' argument about being "led" to choose a crystal growth inhibitor is not persuasive because the rejection is based on anticipation, not obviousness. The Examiner's position is that Liversidge '401 described the claimed composition. The Examiner provided evidence that several of Liversidge 401's cryoprotectants were the same as the claimed crystal growth inhibitors, shifting the burden to Appellants to show otherwise. *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). While Appellants argue the two classes of agents are not equivalent functionally, insufficient evidence has been provided that Liversidge '401's cryoprotectants would not inherently serve as crystal growth inhibitors.

Appellants point out that mannitol and Tween did not prevent crystal growth in certain examples described by Liversidge '401 (FF10; Reply Br. 11). Again, we note that the basis of the rejection is anticipation. The efficacy of these compounds in reducing particle size growth does not alter

the fact that the prior art liquid composition of Liversidge '401, prior to lyophilization, comprised all four components of the claimed composition.

Stability

Appellants contend that the "stable" limitation of claim 1 is not met (Reply Br. 9 & 12).

Based on the identity between the claimed components, the nanoparticle sizes, and Liversidge 401's comparable composition (FF6 & FF7), the Examiner had a reasonable basis for believing that Liversidge '401 met all the limitations of the claim. Appellants contend that Liversidge 401's composition is not "stable," and define stable as having a particle size of less than 2000 nm (Reply Br. 12), but they have not shown error in the Examiner's finding that Liversidge 401's liquid composition, prior to lyophilization, met this particle size limitation (FF6).

Summary

We affirm the rejection of claim 1. Claims 2, 3, 5, 6, 8-19, 21-24, 27-29, 32-35, 37, 39, 41, and 43-45 were not separated argued, and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

ANTICIPATION BY KIPP '329

Issue

The Examiner found that Kipp '329 described all four components of the claimed liquid dosage composition. Appellants contend that the Examiner erred in this determination.

Kipp '329 is a frozen composition

Appellants contend that Kipp '329 describes a "frozen aqueous matrix," not a liquid dosage form as in claim 1 (App. Br. 10).

This argument fails to acknowledge the plain fact that Kipp '329 describes a liquid composition prior to freezing (FF11 & FF12). Consequently, we accord this argument no weight.

Kipp '329 does not teach crystal growth inhibitors

Appellants contend it "is unclear which compound the Examiner deems to teach the osmotically active crystal growth inhibitor of the claimed invention because the Examiner simply cites to paragraph[s] . . . , absent any elaboration on how any of these compounds teaches the claimed crystal growth inhibitor." (Reply Br. 13).

We do not agree. The Examiner identified mannitol as one of Kipp '329's osmotic agents (Answer 7; FF20), which is specifically claimed by Appellants as a crystal growth inhibitor (claim 6). The Examiner also pointed to paragraph 71 of Kipp '329 for teaching cryoprotectants (Answer 7). Mannitol is also specifically listed in paragraph 71 (FF19). Thus, it was quite clear from the Examiner's Answer that either Kipp's osmotic agents or cryoprotectants were considered by the Examiner as anticipating the claimed class of crystal growth inhibitors.

Mannitol is described by Kipp '329 (FF19 & FF20) and characterized in the Specification as a crystal growth inhibitor (Spec. 8:5-9). Appellants' assertion that "Kipp fails to expressly disclose any of the crystal growth modifiers required by the present claims" is therefore not true. (Reply Br. 14).

Summary

We affirm the rejection of claim 1. Claims 2, 3, 5-24, 26-31, 35, 37, 39, 41, and 43-45 were not separated argued, and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

OBVIOUSNESS OVER LIVERSIDGE '401 IN VIEW OF BROCKBANK OR KIPP '329

We adopt the Examiner's fact-finding and reasoning as set forth in the Answer (pp. 8-9). Appellants contend that Liversidge '401 and Kipp '329 were improperly combined because each take different approaches in creating stable nanoparticle compositions (App. Br. 10-11). The Examiner properly responded to this argument by pointing out that Brockbank and Kipp '329 were cited for their teaching that sodium chloride is a cryoprotectant (Answer 13). Because a compound and its properties are inseparable, a person of ordinary skill in the art would have had a reasonable expectation that sodium chloride would retain its inherent function as a cryoprotectant in Liversidge '401 as well. Appellants did not show otherwise.

We affirm the rejection of claims 1-3, 5-24, 27-29, 32-35, 37, 39, 41, and 43-45.

OBVIOUSNESS OVER LIVERSIDGE '401 AND LIVERSIDGE '049

Appellants acknowledge that the rejected dependent claims 25-35, 37, 39, 41, and 43-45 stand or fall together with the rejected base claims (App. Br. 11). As we affirmed the rejection of the base claims, we affirm this rejection as well for the reasons stated by the Examiner.

SECTION 112 REJECTIONS

Appellants did not challenge the propriety of the grounds of rejection under Section 112 (Rejections 5 & 6). Rather, Appellants contend certain procedural actions by the Examiner denied them the "fair opportunity to submit claim amendments" (App. Br. 8).

The Board's jurisdiction is over decisions by a primary examiner to reject claims. 35 U.S.C. § 134(a). Consequently, whether the procedure followed by Examiner was proper is not a matter for us to decide. We affirm the rejections of the claims under Section 112 for the reasons given by the Examiner.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

KMF

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